A facile synthetic route to two chalcones

Zhenting Du, Xuegong She, Junying Ma, Zikun Wang, Huafang Wu, Yang Li and Xinfu Pan*

**State Key Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou 730000, China*

A facile total synthetic route to two naturally occurring chalcones with a partially methylated structure has been achieved in good yield. The key step was selective deprotection of a MOM ether in the aryl methyl ether 6 by a solid phase reaction.

Keywords: chalcone, synthesis, solid phase reaction

Chalcones (1, 3-diphenyl-2-propen-1-one) and bearing oxygen functions on the aromatic rings are the precursors of the flavonoids.[1] Chalcones bearing unnatural substituents have been synthesised recently in order to develop drugs active against cancer[2,3] or malaria[4]. 2', 4'-Dihydroxy-4, 6'-dimethoxychalcone **1** and 4'-hydroxy-4, 2', 6'-trimethoxychalcone **2** are two members of this family. They were isolated from the aerial parts of *Vitex leptobotrys* in North Vietnam.[5] Since the two compounds share a similar partially-methylated multiphenolic motifs, they are difficult to synthesise. To the best of our knowledge, no synthetic work on these two compounds has been reported. Herein we describe an efficient synthetic route to them. Our spectroscopic data agree with those reported previously.[5]

As shown in Scheme 1, 2,4, 6-trihydroxyacetophenone **8** was used as the starting material. It was subjected to selective protection of the 2, and 4-hydroxyl groups with chlorodimethyl ether to afford the acetophenone derivative **7**. The remaining C-6 hydroxyl group was then methylated to give **6**. A to selectively remove the C-2 MOM group, solid phase reaction was used. The crude compound **6** was dispersed with silica gel and the resulting silica gel was ground for 10 minutes. The product was purified directly through column chromatography to give **5** in 97% yield. This result was attributed to the acetyl group which was a good electron-withdrawing moiety and which tended to form a hydrogen bond with the C-2 hydroxyl group. Because of this the C-2 MOM was more reactive and can be removed by these very mild conditions.

Compound **5** was condensed with anisaldehyde in KOH/H_2O/EtOH system to afford the key intermediate **4**. The target chalcone **1** was obtained after removal of the MOM group by an HCl/MeOH system. Compound **4** was further methylated by a phase transfer reaction[6] in the presence of tetrabutylammonium iodide to give another key intermediate **3** which can be converted into **2** easily after being treated with the HCl/MeOH system.

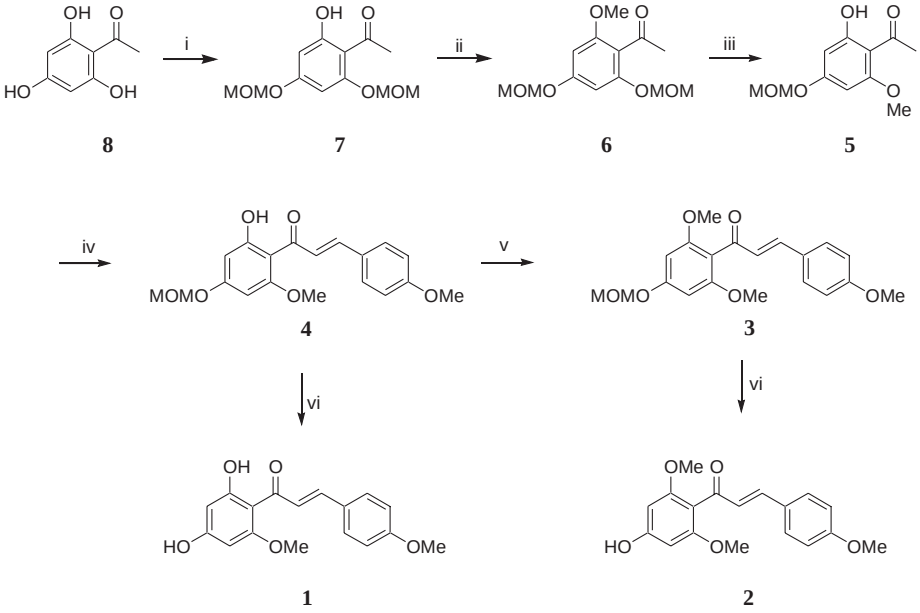
In summary, we have synthesised 4'-OH chalcones **1** and **2** in high yield via six steps in which selective deprotection of a MOM group by solid phase reaction was used. A feature of this approach is that 2, 6-dimethoxy-4-hydroxylacetophenone derivatives can be obtained efficiently.

Experimental

General

The ^1H NMR data were recorded in $CDCl_3$ with Bruker AM-200 or Bruker AC-80 spectrometers if not noted otherwise. The chemical shifts are reported in ppm relative to TMS. Mass spectra were recorded on a HP-5988 mass spectrometer (EI). Column chromatography were generally performed on silica gel (200–300 mesh) eluting with petroleum ether: EtOAc (100:1- 20:1 v/v) and TLC inspections on silica gel GF254 plates with petroleum ether: EtOAc (20: 1- 5:1 v/v) if not noted otherwise.

2, 4-Dimethoxymethyl – 6 – hydroxylaceto phenone, **7**: To a solution of 2, 4, 6-trihydroxy- acetophenone **8** (6.0 g, 35.7 mmol) in anhydrous acetone (180 ml) was added K_2CO_3 (13.8 g, 100 mmol). The above mixture was stirred for 4 h and then the MOMCl (5.5 ml, 74.5 mmol)



Scheme 1 Reagents and conditions: (i) MOMCl, K_2CO_3, acetone, reflux; (ii) Me_2SO_4, K_2CO_3, acetone, reflux; (iii) silica gel, (200–300 mesh), grinding and chromatography; (iv) anisaldehyde, KOH, EtOH, H_2O; (v) NaOH, H_2O, CH_2Cl_2, TBAI, Me_2SO_4; (vi) 3N HCl, MeOH, reflux.

* Correspondence. E-mail: panxf@lzu.edu.cn

was added dropwise. After the addition, the mixture was stirred for 1 h at room temperature and then refluxed for 2 h. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography to give 2, 4-dimethoxymethyl 6-hydroxy acetophenone **7** (5.5 g, 65%) as colourless oil, ^{1}H NMR: 2.51 (3H, s), 3.20 (3H, s), 3.31 (3H, s), 5.22 (2H, s), 5.24 (2H, s), 6.07 (1H, d, *J* = 2 Hz), 6.27 (1H, d, *J* = 2 Hz), 13.8 (1H, s), EIMS(*m/z*): 256 (M^+, 50), 211 (17), 193 (21), 181 (32), 45 (100).

2-Methoxy-4-moethoxymethyl-6-hydroxyl acetophenone **5**: To a solution of **7** (2.0 g, 7.8 mmol) in anhydrous acetone, was added K_2CO_3 (3.2 g, 23 mmol), and Me_2SO_4 (0.8 ml, 8.4 mmol). The mixture was refluxed for 2 h and then quenched with water. The mixture was extracted with ether (3×30 ml). The combined organic layer was washed by brine and dried over $MgSO_4$. The solvent was evaporated and the residue was dispersed by silica gel (200–300 mesh, 2 g) with grinding for 10 minutes. After standing for 2 h, it was purified by column chromatography to give 2-methoxy-4-methoxymethyl-6-hydroxylaceto-phenone **5** (1.6g, 97%) as a white solid, m.p. 78–80°C, ^{1}H NMR: 2.62 (3H, s), 3.51 (3H, s), 3.88 (3H, s), 5.20 (2H, s), 6.04 (1H, d, *J* = 2.4 Hz), 6.24 (1H, d, *J* = 2.4 Hz), 13.84 (1H, s), ^{13}C NMR (75 MHz, $CDCl_3$): 53.97, 56.94, 94.21, 97.33, 107.12, 109.99, 160.56, 163.66, 167.03, 203.46. EIMS (m/z): 226, (M^+, 50), 211 (17), 194 (21), 181 (32), 152 (9), 45 (100). HRMS (ESP positive): 227.0923; Required: $C_{11}H_{15}O_5$, 227.0921.

2'-Hydroxyl-4'-methoxymethyl-4, 6'-dimethoxy chalcone **4**: Under argon, to a cold solution of KOH (3g) in EtOH (2.5 ml) and H_2O (2.5 ml) was added a mixture of **5** (600 mg, 2.65 mmol) and anisaldehyde (370 mg, 2.66 mmol) in EtOH (2 ml). The mixture was stirred for 24 h at 0°C, then 10 ml water was added. The system was extracted with ether (3×30 ml). The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography to give **4** (715 mg, 86%) as a yellow solid, m.p. 122–124°C. ^{1}H NMR (200MHz, $CDCl_3$) 3.51 (3H, s), 3.86 (3H, s), 3.94 (3H, s), 5.22 (2H, s), 6.02 (1H, d, *J* = 2.2 Hz), 6.28 (1H, d, *J* = 2.2 Hz), 6.93 (2H, d, *J* = 8.0 Hz), 7.58 (2H, d, *J* = 8.0 Hz), 7.80 (2H, s), 14.1 (1H, s), ^{1}H NMR (300 MHz, acetone-d6): 3.46 (3H, s), 3.87 (3H, s), 4.01 (3H, s), 5.28 (2H, s), 6.20 (1H, d, *J* = 3Hz), 6.22 (1H, d, *J* = 3Hz), 7.03 (2H, d, *J* = 8.7 Hz), 7.71 (2H, d, *J* = 8.7 Hz), 7.77 (1H, d, *J* = 15.6 Hz), 7.91 (1H, d, *J* = 15.6 Hz), 14.1 (1H, s), ^{13}C NMR (100 MHz, $CDCl_3$): 55.40, 55.88, 56.43, 91.77, 94.07, 96.65, 107.06, 114.37, 125.14, 128.30, 130.12, 142.59, 161.41, 162.56, 163.48, 167.75, 192.80. EIMS(*m/z*): 344 (M^+, 27), 343 (23), 299 (4), 237 (12), 210 (9), 161 (10), 134 (21), 121 (31). HRMS (ESP positive): 345.1328, Required: $C_{19}H_{21}O_6$, 345.1330.

2',4'-Dihydroxy-4, 6'-dimethoxy chalcone 1: To a solution of 4 (100 mg, 0.29 mmol) in methanol (5 ml) was added 3N HCl (0.2 ml). The mixture was refluxed 30 min, cooled to room temperature and extracted with ethyl acetate (3×30 ml). The combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography to give 1 (81 mg, 95%) as a yellow solid, m.p. 168–170°C (Lit.[5] 170–172°C). ^{1}H NMR (300MHz, acetone-d6): 3.87 (3H, s), 3.97 (3H, s), 6.01 (1H, d, *J* = 2.2 Hz), 6.07 (1H, d, *J* = 2.2 Hz), 7.01 (2H, d, *J* = 6.8 Hz), 7.69 (2H, d, *J* = 6.8 Hz), 7.73 (), 7.88 (2H, d, *J* = 15.6 Hz), 14.25 (1H, d, *J* = 15.6 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): 55.34, 55.91, 91.10, 96.79, 107.63, 114.38, 125.13, 128.33, 130.12, 142.57, 161.40, 162.60, 163.21, 167.90, 192.70. EIMS(*m/z*): 300 (M^+, 49), 285 (5), 257 (4), 193 (26), 167 (28), 149 (27), 134 (70), 121 (62). HRMS(ESI positive): 301.1065, Required: $C_{17}H_{17}O_5$, 301.1064.

4'-Methyoxymethyl-4, 2', 6'-trimethoxy chalcone **3**: To a solution of **4** (300 mg, 0.95 mmol) in CH_2Cl_2 (10 ml) was added 10% KOH (10 ml) tetrabutylammonium iodide (20 mg) and Me_2SO_4 (0.3 ml). The mixture was stirred at room temperature for 5 h and then poured into CH_2Cl_2 (30 ml). The organic phase was separated and washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography to give **3** (310 mg, 97%) as a yellow solid, m.p. 112–114°C. ^{1}H NMR (200MHz, $CDCl_3$): 3.53 (3H, s), 3.81 (6H, s), 3.83 (3H, s), 5.21 (2H, s), 6.31 (2H, s), 6.89 (1H, d, *J* = 16 Hz), 6.91 (2H, d, *J* = 6.8 Hz), 7.31 (1H, d, *J* = 16 Hz), 7.50 (2H, d, *J* = 6.8 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): 55.40, 55.88, 56.44, 91.77, 94.08, 114.37, 125.14, 128.30, 130.12, 142.59, 161.40, 162.56, 163.48, 167.75, 192.80. EIMS (*m/z*): 358 (M^+, 16), 343 (6), 330 (46), 285 (18), 225 (6), 195 (8), 161 (16), 121 (12), 45 (100). HRMS (ESI positive): 359.1485, Required: $C_{17}H_{17}O_5$, 359.1483.

4'-Hydroxyl-4, 2', 6'-trimethoxy chalcone **2**: To a solution of **3** (100 mg, 0.28 mmol) in methanol (5 ml) was added 3N HCl (0.2 ml). The mixture was refluxed for 30 min, and cooled then extracted with ethyl acetate (3×30 ml). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography to give **2** (85 mg, 97%) as a yellow solid, m.p. 200–202°C (Lit.[5] 208–210°C). ^{1}H NMR(200MHz, $CDCl_3$): 3.73 (6H, s), 3.84 (3H, s), 6.10 (2H, s), 6.85 (1H, d, *J* = 16 Hz), 6.89 (2H, d, *J* = 8.8 Hz), 7.34 (1H, d, *J* = 16 Hz), 7.48 (2H, d, *J* = 8.8 Hz), ^{13}C NMR (100 MHz, $CDCl_3$): 55.40, 55.83, 92.20, 114.31, 126.92, 127.68, 131.15, 114.50, 158.96, 161.50, 167.22, 168.88, 194.73. EIMS (*m/z*): 314 (M^+, 32), 299 (26), 286 (100), 271 (16), 243 (8), 181 (62), 161 (29). HRMS (ESI): 315.1227, Required: $C_{18}H_{19}O_5$, 315.1234.

We are grateful to the National Science Foundation of China (No. 20172023) for financial support.

Received 11 July 2003; accepted 23 November 2003
Paper 03/2017

References

1 (a) G. Forkmann and W. Heller, *Comprohensive Natural Products Chemistry* Elsevier Science: Amsterdam, 1999, pp.713–748; (b) J.R. Pimmock, D.W. Elias, M.A. Boazely and N.M. Kandem, *Curr. Med. Chem.*, 1999, **6**, 1125.
2 M.L. Edwards, D.M. Stemerick and P.S. Sunkara, *J. Med. Chem.*, 1990, **33**, 1948.
3 F. Bios, C. Beney, A. Boumendjel, A.M. Mariotte, G. Conseil and A. di Pietro, *J. Med. Chem.* 1998, **41**, 4161.
4 M. Liu, P. Wilairat and M.L. Go, *J. Med. Chem.* 2001, **44**, 4443.
5 T.T. Trinh, R. Andrea, R. Helmut, V.S. Tran and A. Gunter, *Phytochemistry*, 1998, **49**, 2603.
6 A. McKillop, J.C. Fiaud and R.P. Hug, *Tetrahedron*, 1998, **30**, 1397.